this application (*see*, e.g., Paper No. 2, page 7 and Paper No. 7, page 3). The Examiner is respectfully requested to enter the amendment.

The Rejections under 35 U.S.C. § 102

Claims 1, 2 and 10-14 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Claffey et al., Biochim. Biophys. Acta., 1246(1):1-9 (1995) (Claffey et al.). Additionally, Claims 1-3, 10-12 and 14 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Pötgens et al., J. Biol. Chem., 269(52):32879-32885 (1994) (Pötgens et al.). Applicants respectfully traverse the rejections because the cited references do not disclose a variant VEGF polypeptide that is a VEGF antagonist molecule.

The presently claimed invention is directed to VEGF antagonist molecules comprising VEGF variant polypeptides having at least one modified cysteine residue which inhibits the molecules from properly dimerizing with other VEGF monomers. These antagonist molecules are capable of binding VEGF receptors without significantly inducing a VEGF response and inhibiting a biological activity of a native VEGF.

Claffey et al. teach a variety of murine VEGF mutants that are incapable of inducing VEGF activity. Specifically, in Figure 7, Claffey et al. disclose that a variety of mutants of VEGF have no biological activity, based on vascular permeability assay. However, the Claffey et al. disclosure does not teach, suggest nor even contemplate that these mutant VEGF molecules effectively function as a VEGF antagonist as presently claimed. Specifically, Claffey et al. do not disclose nor suggest that any of their mutants are capable of binding to a VEGF receptor or inhibiting a biological activity of a native VEGF protein.

Like Claffey et al., Pötgens et al. also disclose mutated VEGF polypeptides. And, like Claffey et al., Pötgens et al. also do not teach nor suggest that such variant polypeptides would act as VEGF antagonists, i.e., that they are capable of inhibiting a biological activity of a native VEGF protein.

The Office Action states that the molecules disclosed by these two references inherently possess all of the characteristics of the instant VEGF antagonists and anticipate the present claims, "absent clear and convincing evidence to the contrary" (page 8 of Office Action mailed 7/7/97 (paper 2)). While Applicants submit this is not the proper standard, *arguendo,* such evidence is presented.

The Examiner is respectfully directed to page 32883, column 1 of Pötgens et al., 1994. The investigators specifically addressed the question of antagonist activity of the disclosed VEGF variants to wild type VEGF. They found that "[i]n no case did any mutant inhibit the activity of the wild type protein." Clearly, the molecules disclosed by Pötgens et al. are not molecules of the present invention, and this reference does not anticipate the present claims.

In light of the disclosure of Pötgens et al., the possible inherency of the Claffey et al. molecules to act as antagonists to VEGF fails to meet the standard for inherency. Although a prior art article may inherently have the characteristics of the claimed invention, this is not sufficient to support a rejection under 35 U.S.C. § 102; rather, the inherency must be certain. See Ex parte Skinner, 2 USPQ2d 1788 (BPAI 1986) and Ex parte Cyba, 155 USPQ 756 (POBA 1966). Moreover, "inherency must be a necessary result and not merely

a possible result". In re Oelrich, 212 USPQ 323 (CCPA 1981) (emphasis supplied). In the case of Claffey et al., the required certainty is not shown to support the present rejection. Specifically, as discussed above, Claffey does not disclose binding to a VEGF receptor or inhibition of native VEGF activity. Moreover, Pötgens supports that mutants can be made which are not antagonists.

For the reasons stated above, Applicants respectfully submit that Claffey et al. and Pötgens et al. do not inherently anticipate the presently claimed invention under the applicable case law as described above. Particularly, Pötgens et al. shows that VEGF mutants can be made that do not inhibit VEGF activity. In contrast, the presently claimed VEGF antagonists are capable of binding to VEGF receptor, and inhibiting biological activity of a native VEGF. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102.

The Rejections under 35 U.S.C. § 103

Claims 4-6, 9 and 13 stands rejected under 35 U.S.C. § 103(a) as being "unpatentable" over Pötgens et al. Additionally, Claims 7 and 8 stand rejected under 35 U.S.C. § 103(a) as being "unpatentable" over Pötgens et al. in view of Pang, U.S. Patent No. 5,418,135 (Pang). Applicants respectfully traverse the rejections.

To establish a *prima facie* case of obviousness, the prior art must 1) disclose all of the present claim limitations, 2) suggest either modifying or combining the prior art disclosure to obtain the present invention, and 3)

provide a reasonable expectation of success that the present invention would be obtained.

The Pötgens et al. reference is discussed above. As discussed above, this reference does not disclose antagonist molecules that inhibit biological activity of a native VEGF protein. In fact, the molecules described by Pötgens et al. were specifically shown not to inhibit native VEGF biological activity. With this finding, Pötgens et al. teaches away from modifying its disclosure to obtain an antagonist molecule capable of inhibiting a biological activity of a native VEGF protein. As such, no reasonable expectation of success in obtaining the presently claimed antagonist molecule can be found from Pötgens et al.

Pang does not cure the shortcomings of the Pötgens et al. reference. Pang discloses the use of polypeptides having some homology to a portion of a platelet derived growth factor (PDGF) to antagonize the activity of PDGF. This reference is not directed to antagonist molecules of VEGF nor variant VEGF polypeptides, it is not directed to VEGF receptors or biological activity of VEGF in any way. Furthermore, Pang does not teach the modification of at least one cysteine residue or inhibition of a polypeptide monomer to dimerize.

Neither Pötgens et al. nor Pang, alone or in combination, disclose all of the claim limitations of the present claims. Lacking these disclosures, no motivation is provided to combine the teachings of Pang and Pötgens et al., nor is any expectation of obtaining the presently claimed invention. Therefore, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections under 35 U.S.C. § 103.

On the basis of the amendment and the remarks presented herein, we believe that this application is now in condition for immediate allowance and respectfully request the Examiner to withdraw the outstanding rejections and pass this application to issue.

Respectfully submitted,

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APPENDIX

1. (Twice Amended) A vascular endothelial cell growth factor (VEGF) antagonist molecule comprising a variant VEGF polypeptide, said variant polypeptide comprising an amino acid modification of at least one cysteine residue, wherein said amino acid modification inhibits the ability of said variant polypeptide to properly dimerize with another VEGF polypeptide monomer, wherein said antagonist molecule is capable of binding to VEGF receptors without significantly inducing a VEGF response, wherein said antagonist molecule is capable of inhibiting a biological activity of a native VEGF protein.

2. The antagonist molecule according to Claim 1 wherein said amino acid modification is a substitution of said at least one cysteine residue with a different amino acid which is incapable of participating in a disulfide bond.

3. The antagonist molecule according to Claim 2 wherein said substitution is of the cysteine residue at amino acid position 51 and/or 60 of the native VEGF amino acid sequence.

4. The antagonist molecule according to Claim 3 wherein aspartic acid is substituted for cysteine.

5. The antagonist molecule according to Claim 4 comprising the substitution C51D.

6. The antagonist molecule according to Claim 4 comprising the substitution C60D.

7. The antagonist molecule according to Claim 1 wherein said amino acid modification is a chemical modification of said at least one cysteine residue which renders said cysteine residue incapable of participating in a disulfide bond.

8. The antagonist molecule according to Claim 7 wherein said chemical modification is of the cysteine residue at amino acid position 51 and/or 60 of the native VEGF amino acid sequence.

9. The antagonist molecule according to Claim 1 containing further amino acid modifications that do not otherwise affect the essential biological characteristics.

10. An isolated nucleic acid sequence comprising a sequence that encodes the VEGF antagonist molecule of Claim 1.

11. A replicable expression vector capable in a transformant host cell of expressing the nucleic acid of Claim 10.

12. Host cells transformed with the vector according to Claim 11.

13. Host cells according to Claim 12 which are Chinese hamster ovary cells.

14. A composition of matter comprising the VEGF antagonist molecule according to Claim 1 compounded with a pharmaceutically acceptable carrier.